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Use of a Third Dose of the Measles Mumps Rubella Vaccine during Mumps Outbreaks

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Among the actions considered by the Advisory Committee on Immunization Practices (ACIP) during their October 2017 meeting was a recommendation for administration of a third dose of the measles, mumps, rubella (MMR) or MMR with varicella (MMRV) vaccine in the setting of a mumps outbreak.[1] This recommendation comes as the result of a significant increase in the number of mumps outbreaks in the United States over the several years. After a period for public comment, the recommendation was unanimously approved by the ACIP in January 2018.

In their report published in the January 12th issue of *Morbidity and Mortality Weekly Report*, Marin and colleagues described a substantial increase in cases since 2012, with 6,369 cases in 2016 and 5,629 in 2017.[2] The data, collected from state health departments throughout the country, revealed 150 mumps outbreaks (defined as 3 or more cases of mumps linked by time and place) between January 1, 2016 and June 20, 2017. These outbreaks alone accounted for 9,200 cases. Seventy-five (50%) of the outbreaks occurred at universities. The median number of cases per outbreak was 10, with 20 outbreaks (13%) accounting for more than 50 cases. Most cases involved young adults, with a median age at diagnosis of 21 years. Among the patients with a complete vaccination record, 78% had received 2 doses of MMR during childhood.

Mumps Infection

The mumps virus, a paramyxovirus, belongs to the genus *Rubulavirus*. There are currently 12 recognized genotypes of the virus, designated as types A through N.[2,3] Since 2006, genotype G has been the most common cause of mumps cases worldwide. Virulence is known to be associated with both hemagglutinin-neuraminidase (HN) and fusion surface proteins. Mutations in the HN protein have been associated with an increased likelihood of neurological complications.

Mumps infection often begins with a nonspecific prodrome of low-grade fever, myalgias, malaise, anorexia, and headache.[2-4] The most common clinical indicator of mumps infection is parotitis, occurring in approximately 70-85% of patients. Parotitis often begins 1-2 days after the onset of symptoms, with swelling of the lower part of the ear which then continues to extend downward into the face and neck. Swelling typically peaks within 1-3 days and resolves over 7-14 days without intervention. Approximately 10-20% of patients will remain asymptomatic or have only nonspecific respiratory symptoms after infection. All patients with the virus, including those with no obvious symptoms, are contagious. The virus is transmitted through direct contact, droplet spread, or contaminated surfaces.

More severe manifestations of mumps infection include orchitis, occurring in 10-66% of unvaccinated males, with aseptic meningitis and encephalitis in 0.2-10% and 0.02-0.3% of unvaccinated patients, respectively.[2] Pancreatitis, deafness, and oophoritis or mastitis in females have been reported in less than 1% of patients.[4] These complications may also occur in previously immunized patients who develop a mumps infection, but much less frequently. An estimated 3-11% of immunized patients experience parotitis, and less than 1% develop aseptic meningitis or encephalitis. Death from mumps infection is extremely rare.[2]

MMR Vaccine

Prior to the development of an effective vaccine, there were 150,000-200,000 cases of mumps each year in the United States. Implementation of

routine childhood immunization has led to an estimated 99% decrease in cases. The MMR vaccine is a sterilized preparation of attenuated live measles virus derived from the Edmonston genotype A strain, mumps virus derived from the Jeryl Lynn (B level) strain, and Wistar RA 27/3 strain of attenuated rubella virus.[5] A single injection of the vaccine induces measles hemagglutination-inhibition (HI) antibodies in 95% of patients, mumps neutralizing antibodies in 96%, and rubella HI antibodies in 99%. Recent studies have confirmed the effectiveness of immunization at 12-15 months and 4-6 years with the current MMR vaccine in producing adequate neutralizing antibody titers against the genotype G strain, the most common cause of illness. The geometric mean antibody titer (GMT) for genotype G, however, is typically lower than the GMT for genotype A, the strain used in preparing the vaccine.[6,7]

Antibody persistence is known to wane after MMR immunization. It has been estimated that titers decline by approximately 3% per year, with a considerable degree of variation among patients. Earlier this year, Seagle and colleagues reported data on antibody titers from a 12-year longitudinal study of 302 children given their first dose of the MMR vaccine at 4-6 years of age.[8] The majority of children remained seropositive for the duration of the study, with 96%, 88%, and 79% of the children seropositive to measles, mumps, and rubella, respectively, at last follow-up. The GMT to measles declined by an average of 9.7% per year, while the GMT to mumps declined 9.2% per year. The decline in GMT for rubella was slower and differed by the time of administration. Children receiving their first MMR dose at 12-15 months had a decline in GMT of only 2.6%, compared to 5.9% in children who received their first dose at more than 15 months of age. No predictors were found for the high rate of decline in the measles and mumps vaccines.

A decrease in mumps seropositivity over time was also demonstrated in a retrospective study of antibody titers obtained from 3,811 United States military recruits at the outset of training.[9] A nonlinear decline was seen in samples analyzed with the BioPlex 220 MMRV IgG multiplex flow immunoassay, with a sharp decrease seen at 13 years from administration of the recruits' last dose of MMR. Seropositivity fell below the level needed to maintain herd immunity in the recruits who received their last dose more than 16 years prior to enlistment.

Effectiveness of a Third Dose during Outbreaks

Experience with the administration of a third dose of the MMR vaccine comes from a number of reports of outbreaks at universities, close communities, and military bases. The first study to describe the impact of an additional MMR dose to control a mumps outbreak was published in *Pediatrics* by Ogbuanu and colleagues.[10] A total of 1,755 children (6^{th}-12^{th} grade) from three schools were given a third dose of the MMR vaccine during the 2009-2010 mumps outbreak in and around a village populated by several Orthodox Jewish communities in Orange County, New York. Among the school children, mumps attack rates declined from 4.93% prior to the start of the program to 0.13% after implementation ($p < 0.001$). The attack rate declined by 75.6% village-wide.

Nelson and colleagues described the impact of a third MMR dose on a mumps outbreak in Guam during the same 2009-2010 period.[11] The authors instituted an active surveillance program, administering the vaccine to students 9-14 years of age at seven schools with the highest attack rate. A total of 505 cases of mumps were reported between December 1, 2009 and December 31, 2010. Of those cases 287 were in school-aged patients, with 270 (93%) having had at least 2 doses of MMR. A third dose was administered to 1,068 students, resulting in a 60% decrease in the attack rate which, while clinically important, failed to reach statistical significance (0.9/1000 compared to 2.4/1000 among students who did not receive a third dose, $p = 0.67$).

Cardemil and colleagues documented the effectiveness of a third MMR dose during the 2015-2016 mumps outbreak at the University of Iowa in the September 7, 2017 issue of the *New England Journal of Medicine*.[12] Of the 20,496 students enrolled, 98.1% had previously received at least two doses of the MMR vaccine. Students who had received their second dose of MMR more than 13 years prior to the outbreak were more than 9 times more likely to be diagnosed with mumps. During the outbreak, 4,783 students elected to receive a third dose. The subsequent attack rate was significantly lower in those who had the third dose (6.7 versus 14.5 cases/1000 population, $p < 0.001$). At 28 days post-dose, students had a 78.1% lower risk of mumps than those who had not received a third dose (adjusted hazard ratio 0.22; 95% CI 0.12-0.39).

In a subsequent article on the same outbreak in *Clinical Infectious Diseases,* Shah and colleagues, writing for the Iowa Mumps Outbreak Response Team, described the containment project the University as well as the surrounding community.[13] Their report not only documents the benefit of a third dose of MMR vaccine, but also provides considerable insight into how an

outbreak develops and the impact of prompt recognition and containment. This article is a very useful reference for other institutions developing containment strategies.

In a Letter to the Editor written in response to the 2017 Cardemil paper, Jent, Olah, and Sommerstein described their analysis of a mumps outbreak in Swiss military recruits.[14] In September 2017, 26 cases of mumps were reported in a company of 140 recruits in a single compound. This corresponded to an overall 18.6% attack rate in a population where 91.4% of the individuals had received two or more doses of the MMR vaccine. Separating out the data, the attack rate was 86% in the unvaccinated soldiers, 15.4% among those who had received two doses of MMR, and 8.3% in those who had received a third dose.

Impact of a Third Dose on Antibody Titers

Latner and colleagues evaluated the effect of a third dose of MMR given to 656 healthy young adults (18-28 years of age) participating in a longitudinal study of immune response to vaccination.[15] Participants provided serum samples at prior to a third MMR dose and at one month and one year post-dose. The data revealed a modest, but statistically significant, increase in mumps antibody titers, as measured by enzyme-linked immunosorbent assay (ELISA) using the whole mumps virus, as well as just the HN and fusion surface proteins. One year after immunization, mumps antibody titers had declined, but remained significantly above baseline ($p < 0.05$ for all assessments). The authors concluded from their results that a third dose of MMR should be beneficial during outbreaks, particularly for those patients with very low neutralizing antibody titers, but that routine administration to increase overall population immunity to mumps was not warranted.

Contraindications and Warnings

As with routine immunization, administration of the MMR vaccine during an outbreak is contraindicated in pregnant women and in patients with previous hypersensitivity reactions to any of its components, including gelatin.[5] It should not be administered to patients with a history of severe hypersensitivity reactions to eggs, including hives, angioedema, mouth and throat swelling, difficulty breathing, or shock. It may be considered for patients with less severe reactions. Although the American Academy of Pediatrics recommends against giving the measles vaccine to patients with a history of an allergic reaction to neomycin, it is not considered an absolute contraindication. Patients with a history of dermatitis after being exposed to neomycin may develop a pruritic rash after MMR administration.

While the vaccine may be given to patients with minor illness (mild upper respiratory infections, low-grade fever, or diarrhea), it should not be administered in patients with an acute febrile illness.[5] The MMR vaccine should not be given to patients receiving immunosuppressive therapy (excluding corticosteroid replacement therapy) or to those known or suspected to have primary or acquired immunodeficiency diseases who are clinically immunosuppressed. Administration of attenuated measles virus to immunocompromised individuals inadvertently has resulted in pneumonitis, and measles inclusion body encephalitis (MIBE). Patients previously diagnosed with thrombocytopenia who receive the MMR vaccine may have a worsening of their condition.

Adverse Reactions

The MMR vaccine is generally well tolerated. Adverse reactions reported in more than 1% of patients receiving the MMR vaccine include injection site pain, redness, or swelling, dizziness, fever, rash, and transient arthralgias or arthritis.[5] The likelihood of developing transient arthritis and arthralgias is significantly greater in adults than in children (12-26% versus 0-3%). The rate of these reactions in adolescents is believed to fall between these ranges. Rare, but serious, adverse effects include hypersensitivity reactions (anaphylaxis and anaphylactoid reaction, angioedema, and bronchial spasms), encephalitis, encephalopathy, Guillain-Barré syndrome, seizures, MIBE, pneumonitis, thrombocytopenia, and chronic arthralgias or arthritis.

The incidence of adverse reactions after a third dose of the MMR vaccine is similar to those observed after routine immunization. Abedi and colleagues evaluated the adverse effects reported after administration of a third dose of the MMR vaccine to children in three schools in New York during the 2009-2010 outbreak.[16] In addition to reviewing physician records and the Vaccine Adverse Evens Reporting System (VAERS), the authors surveyed families of the 1,755 children. A total of 91% of families returned the survey, with 115 (7.2%) reporting an adverse reaction within 2 weeks of vaccination. The most commonly reported reactions were pain, redness, or swelling at the injection site (3.6%), joint or muscle aches (1.8%), dizziness or lightheadedness (1.7%), and fever (1.3%). No serious adverse reactions were reported.

The CDC will continue to monitor both the efficacy and safety of a third MMR dose.[2] As with any immunization, potentially serious adverse reactions after use of MMR during an outbreak should be reported to VAERS at https://vaers.hhs.gov/ or 1-800-822-7967.

Administration and Storage

Administration of the MMR vaccine during an outbreak requires careful attention to preparation and storage to ensure vaccine potency is maintained. The MMR vaccine is prepared as a lyophilized powder compacted into a cake which requires reconstitution with the supplied diluent before use.[5] No other substances should be used to dilute the dose. The lyophilized cake must be fully dissolved, and the resulting solution examined to identify any precipitants prior to administration. The vaccine must be refrigerated; however, the diluent may be refrigerated or stored at room temperature. It must be protected from light; exposure to light can inactivate the viruses.

The vaccine should be administered as soon as possible after reconstitution. If this is not possible, the reconstituted vaccine may be stored protected from light in the refrigerator for 8 hours. A dose of 0.5 mL should be administered subcutaneously, preferably in the outer aspect of the upper arm. Administration of the MMR or MMRV vaccine should be separated from the administration of other live virus vaccines by at least one month.

During a mumps outbreak, patients 12 years of age and older may be given a third dose of MMR using either the MMR or MMRV vaccine. Women of childbearing age who receive a third MMR dose for an outbreak should be advised to avoid becoming pregnant within 3 months of receiving either vaccine, due to the exposure to live rubella virus.

Summary

The MMR vaccine provides a high rate of seroconversion to protect children from measles, mumps, and rubella infections, however, its efficacy wanes over time. The growing number of mumps outbreaks in the United States each year, particularly at universities or in other close communities, along with new studies supporting the effectiveness of an additional dose for short-term protection, have led to the recent ACIP recommendation for a third dose of MMR or MMRV to patients at risk. Additional epidemiologic studies will be needed to determine the effectiveness of this new recommendation.

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